REMARKS

Claims 1 - 129 are pending in the application. No claims have been amended. No new claims have been added. Claims 2 – 4, 6, 8 – 11, 16, 19, 20, 22 - 129 have been previously cancelled. No new matter has been added by virtue of these amendments; support therefore can be found in throughout the specification and original claims of the application.

Any cancellation of the claims should in no way be construed as acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Rejection of Claims 1, 3 – 5, 7, 12 – 15 and 17 Under 35 USC 103(a)

The Examiner has maintained the rejection to claims 1, 3 – 5, 7 12 – 15 and 17 under 35 USC 103(a) as being unpatentable over Dominguez et al. (J of Immunological Methods, 1998, 220: 115 – 221) in view of Hooper et al. (USPN 6, 451, 309; the '309 reference herein). Applicants respectfully traverse the rejection.

The instant claims recite a method comprising incubating a mixture comprising at least one cell, a labeled invasin that encodes a detectable label, wherein the labeled invasin is a virus, and a candidate agent under conditions wherein the labeled invasin can invade the cell; and detecting the detectable label within the cell, wherein a decrease of detectable label in the cell due to the candidate agent indicates that the candidate agent decreases invasion of the cell by the invasin.

In response to Applicant's arguments, the Examiner argues that "the combined teachings result in a method that looks at the ability of an antibody to interfere with the infection of cells by using a vaccinia virus/GFP infection marker. This translates to a method that measures protection of cells against virus invasion by measuring a decrease in invasion by a candidate agent." (Office Action, p.3).

In response to Applicant's arguments, the Examiner argues that the specification discloses that a mouse lethality model (SCID mice) was used to show that in vitro neutralization assays correlated positively with significant difference in protective efficiency against lethal infection of mice with vaccinia (and) the ability of the in vitro neutralization assay as a predictor of neutralization has nothing to do with the claimed method because the neutralization assay is not recited in the claims." (Office Action, p.4). Applicants disagree.

Applicants wish to clarify the Examiner's understanding of the claimed method, that is, in fact, directed to a neutralization assay. Applicants direct the Examiner first to page 1, line 26 of the specification that recites "antibody binding to a pathogen that disallows productive infection by the pathogen **is called neutralization**." (emphasis added). Neutralization, as taught in the "background of the invention" section is a well known term of in the field of immunology, and consists of a decrease in the infectious titre of a viral preparation following its exposure to antibodies.

The present invention is directed to the development of a novel assay to measure protection of cells against virus invasion; a novel neutralization assay. As taught in the specification, the method as claimed is the only validated alternative method to the classical labor intensive Plaque Reduction Assay (PRNT). As taught in the specification (e.g. page 46, beginning at line 26) results obtained using beta-gal in the instantly claimed method, are comparable to results obtained with the classic PRNT vaccinia neutralization assays. Moreover, as taught in the specification, the high throughput technology makes the claimed method highly sensitive (e.g. page 47, beginning at line 14), easier to conduct (even with small volumes), faster, and easy to transfer to other laboratories (e.g. page 39, beginning at line 39).

The Dominguez reference teaches the construction of recombinant vaccinia expressing GFP for detection of cells by flow cytometry. However, the construct as taught by Dominguez, is merely used "as an infection tag" and "is useful for studying tropism." Dominguez does not disclose the use of the construct for testing the anti-viral activity of candidate agents, particularly antibodies.

The '309 reference (Hooper) does not cure the flaws of the Dominguez reference.

It would not have been obvious to use the monoclonal antibodies as taught by the '309 reference in the methods of Dominguez, as Dominguez only teach recombinant vaccinia expressing GFP for detection of cells by flow cytometry. Dominguez do not teach a method to measure protection of cells against virus invasion by measuring a decrease in invasion by a candidate agent, but rather teach a method to identify potential targets and cell tropism of the virus.

No combination of Dominguez and the '309 reference teaches the method as instantly claimed, in particular a method to measure protection of cells against virus invasion by measuring a decrease in invasion by a candidate agent.

The methods of the present Application provide a **prediction of virus lethality** that is not possible with the methods taught by either Dominguez or Hooper either alone, or when taken alone or in combination.

As described previously, Applicants have shown that the claimed method is predictive of lethality, for example at page 10 of the specification, and in Example III:

> In order to further establish the in vivo biological correlation of the in vitro neutralization assays of the invention, a mouse lethality model using SCID mice has been established. The difference in neutralization titer observed in the beta-Gal assay correlated positively with significant difference in the protective efficiency against lethal infection of SCID mice with vaccinia (Wyeth). (page 10, line 21 – 28).

Dominguez merely teach "the usefulness of GFP as an infection marker" (p. 120), not as a marker that would be useful in neutralization assays that are predictive of virus lethality as claimed. .

Further, as pointed out by the Examiner, the '309 reference only teaches the production and potential activity of the monoclonal antibodies against vaccinia. The '309 reference does not teach or suggest a reporter-based- assay (for example, B-

galactosidase vaccinia virus or GFP-expressing vaccinia) to demonstrate the protective activity of their monoclonal antibodies.

Accordingly, Applicants respectfully request that the rejection be withdrawn.

Rejection of Claims 18 and 21 Under 35 USC 103(a)

The Examiner has maintained the rejection to claims 18 and 21 under 35 USC 103(a) as being unpatentable over Dominguez et al. (J of Immunological Methods, 1998, 220: 115 – 221) in view of Hooper et al. (USPN 6, 451, 309; the '309 reference herein) as applied to claims 1 and 17, above, and further in view of Englemayer et al. (The J of Immunology, 1999, 163: 6762 – 6768). Applicants respectfully traverse the rejection.

As set forth above, the combination of the Dominguez and the '309 reference fail to teach the invention as claimed. The Englemayer reference does not cure the flaws of the Dominguez and the '309 references.

No combination of the cited art teaches the method as instantly claimed, in particular a method to measure protection of cells against virus invasion by measuring a decrease in invasion by a candidate agent. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Early consideration and allowance of the application are earnestly solicited.

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Respectfully submitted,

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